CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

California Institute for Regenerative Medicine (CIRM)
Strategic Planning Advisory Committee Meeting
June 13, 2006

The third meeting of the Strategic Planning Advisory Committee (SPAC) included a progress report on interviews and meetings conducted to date as well as a discussion centered on two topics: cord blood banking and databanking for human embryonic stem cell (hESC) lines as a possible focus areas for early funding. In the course of this meeting, a number of ideas arose which are summarized below. This summary is not intended to be comprehensive with respect to reporting these ideas; inclusion in this summary does not imply any commitment or endorsement by the CIRM.

A. Progress Report

1. Update on Interviews

a. To date, 21 individuals have been interviewed.
b. A summary of findings from the interviews will be provided at the appropriate time.
c. The CIRM has had over 200 names suggested for interviews and continues to take suggestions.
d. The data collection period of the strategic planning process is anticipated to be completed by the end of July / middle of August.

2. Update on Meetings

a. July 13th scientific conference for the Independent Citizen's Oversight Committee, ICOC, and the public
   i. The information packet and list of speakers for the upcoming July 13 scientific conference were reviewed.
   ii. Members of the Scientific and Medical Research Funding Working Group have been invited to this meeting and eight have confirmed that they will attend.
b. June 2nd ICOC Meeting
   i. A discussion with the ICOC and the public regarding the mission statement and objectives for the CIRM Scientific Strategic Plan was held the evening of June 1.
   ii. Slides from this meeting were provided to the SPAC; the first four contain suggestions for the mission statement, which will be revisited with the ICOC at a later time.

iii. The CIRM's long-term objectives will focus on clinical, translational, and basic science and infrastructure. Several of the objectives suggested during the interview process and during the ICOC discussion were shared with the SPAC, with the understanding that these statements will continue to be refined and brought back to the ICOC for further discussion.

iv. During the next meeting of the ICOC (August 1 and 2) the topic of the values for the strategic plan will be discussed.

c. A question arose about the mission statements contained on the slides and the main themes to come out of the ICOC discussions.

i. All the mission statements presented on the slides were developed during the meeting on the evening of June 1.

ii. As a result of ICOC discussion was that it might also be appropriate to have a preamble to the mission statement. The preamble will explain what we are about but the mission statement will define who we are and where we are going in a brief and concise manner.

iii. The mission statement should be concise and definitive and, in conjunction with 5 or 6 core values, should provide a framework for CIRM's activities.

B. Discussion Topics - Cord Blood Banking

1. An overview of cord blood banking was provided. Dr. Hall mentioned that the information provided represents a sample of what is out there and is not comprehensive or authoritative, but is a starting point for discussion.

a. There are a number of banks in California, some public and some private. Some are in academic medical centers and others are free-standing private banks.

i. For example, there is a public bank in Oakland associated with Children's Hospital of Oakland and a private bank, StemCyte, in Los Angeles.

ii. UCLA started a bank, but it was subsequently closed and all the samples were sent to a repository in Gaithersburg, Maryland. These samples are available to researchers but not for transplants. The bank is now a static collection with no new samples being added.

2. There is increasing regulation of cord blood banks.

a. Post meeting information: As of 2004, all cord blood banks were required to register with the FDA. As of May 2005, the FDA minimally required that all banks which handle human cells and tissue, including cord blood, must follow federal safety standards as set out by the FDA with the primary purpose of preventing the transmission of infectious agents. These regulations outline specific steps banks and laboratories must take when they are processing the cord blood. These regulations apply to the collection, processing, packaging, labeling, and distribution of the cells. Additionally, under this new regulation, cord blood banks must notify the FDA of specific adverse reactions from the stem cells that they process and must allow FDA inspections. Prior to this regulation, voluntary accreditation by an organization such as the American Association of Blood Banks or the Foundation for the Accreditation of Cellular Therapy was the

indicator that a particular blood bank has achieved a high level of commitment, quality, and efficiency in their procedures and practices.

3. A question was raised about the number of transplants done using cord blood.
   a. The number of transplants for 2005 can be obtained from the International Bone Marrow Transplant Registry.
   b. Post meeting information: There have been about 6,000 unrelated-donor cord blood transplants world wide since the inception of cord blood transplantation (J. Clin. Invest 2005:115, 2592). Data from the National Cord Blood Program of the New York Blood Center, which has provided cord blood for about 2,000 of the above mentioned 6,000 transplants, indicates that 74% of the cord blood units it provided were for transplants in the US; the remaining 26% of units were for transplants outside of the US (http://www.nationalcordbloodprogram.org/).

4. There is an increasing recognition that cord blood is a viable alternative to bone marrow for transplantation, at least for children, in those cases where allogeneic hematopoietic stem cell transplantation is needed.
   a. There are some limitations to the use of cord blood, with significant ones being the number of samples that are available as well as compatibility, genetic diversity, immunological concerns, and standardization; additional funding may help people pursue these questions.

5. The SPAC discussed the opportunities in this area, whether it is an important area for CIRM, and what its role should be.
   a. Cord blood transplantation has a variety of applications today, primarily in the context of life-threatening disorders that can be addressed by hematopoietic reconstitution. Cord blood is easily harvested, but the volume (cell number) of individual cord blood units means these treatments are most suitable in the pediatric setting. Experimental studies are exploring the pooling of more than one unit for use in larger children/adults.
   b. CIRM's first priority is to fund research, not to be a provider of cellular therapeutic product, so any effort in the area of cord blood transplantation will focus on research.
   c. There is evidence of the effectiveness of cord blood therapies; perhaps CIRM's role is to support research into enhancing the effectiveness of these therapies or finding ways to amplify cord blood –derived stem cells for use in adults.
   d. Stringency requirements for matching for unrelated-donor transplants appear to be less with cord blood than with adult marrow or mobilized peripheral blood.
   e. Cord blood represents a near-term but still experimental therapy, so very few centers aggressively pursue cord blood transplants. For example, there are a number of experts in bone marrow transplantation but few who pursue cord blood transplantation. CIRM could help to build a clinician/translational scientist community around cord blood that could provide a framework for the additional (stem) cell therapies. (NOTE: This comment was provided by the Chairman of a Scientific Advisory Board of a private, cord blood company.)

6. The concept of the State enacting regulations to collect and type every child's cord blood was discussed.
    a. It is unclear if there is a need for such regulations or a need to collect sample from all newborns as this may not be necessary to make sure there are enough samples for transplantation.

7. Issues related to the use of cord blood
    a. There are ethnic disparities in the area of cord blood collection and banking. For example, patients of Scandinavian decent have better odds of finding a donor, while patients who are African-American or are Orthodox Jews have lower odds of finding a match.
    b. In some ways, the issue is less about the number of samples but rather the number of cells in the sample. Once a sample is used, it is gone, but if there were effective ways to expand the number of cells, cord blood use in transplantation might be expanded.
        i. If there are not enough cells in a given sample, very recent studies indicate that cord blood samples from different donors can be mixed prior to transplantation and still generate a response.
        ii. There are no methods to successfully expand cord blood stem cells to date, as cell differentiation occurs with expansion; there is much work to be done to understand how to expand cells without differentiation.

8. Given the importance of having a clinical network for bone marrow transplants, a question was raised about whether there was a need to create a clinical research community that would carry out cord blood testing or if there should be an extension of existing bone marrow networks to include a larger cord blood effort.
    a. There are benefits to taking advantage of existing infrastructures. CIRM could play a role in supporting this effort and take advantage of existing bone marrow centers.
    b. There is a need for a regulatory infrastructure and a survey of what is in place in state.

9. A question was raised about the source of cord blood stem cells, specifically, whether having a transplant program requires setting up a banking service to go along with it.
    a. The problem with cord blood processing is the need to realize economies of scale, so there is some financial attractiveness to partnering with entities that have already have cord banking facilities.
    b. Organizing, collecting, and transferring the units to a central processing facility for long term storage is complicated and costly; public banks are trying to finance their maintenance and storage costs by releasing a small number of sample per year at ~$10,000/sample.
    c. Donors cannot be accommodated unless there is an infrastructure in place at a given hospital to collect the cord blood sample.

10. A question was raised about the costs of bone marrow versus cord blood transplantation.
    a. The "bare bones" cost to process a cord is $300-$400; the cost of aphoresis (for mobilized peripheral blood stem cells) is $1,000-1,500, while the cost of a bone marrow aspiration would be in the $1,500 range.
    b. It was noted that Health Resources and Services Administration will be funding the set-up of a national cord blood bank for mainly clinical but some research use as well. CIRM should watch how that bank develops before duplicating HRSA's efforts. Money could more productively focused on research activities to expand the ability to use cord blood.
    c. Transplantation itself is a very expensive procedure

11. Developing effective cord blood transplantation for a number of genetic diseases and even leukemia falls into the category of delivering therapies.
    a. It may be a way to serve the unmet need of families in California as it is a near term therapeutic opportunity and may be a way to build a clinical transplant infrastructure for other stem cell therapies.

12. A question was raised about the risk profile of the opportunities available to CIRM in the area of cord blood banking and transplantation.
    a. Any clinical effort would need oversight by an Institutional Review Board and a Disease Safety Monitoring Board and the consent forms would need to indicate the risks of complications from a transplant.
    b. Most patients who undergo invasive trials do so with improving outcomes as a goal and accept the associated risks.
    c. Insurance carriers are reluctant to fund transplants, but if there were publications showing improvements to life expectancy, quality, and productivity, this could lead to greater acceptance of these therapies.
    d. The affordability of these treatments will also be important.

13. A question was raised about whether it would make sense to have a single bank for cord blood samples and hESC lines.
    a. Infectious disease screening was cited as one factor that makes this impractical. Also, while running a cord blood bank is like running a regular blood bank, simply growing hESC lines is a different league of complexity, so they should probably be kept separate.

14. A question was raised about whether HLA typing is performed on newborns.
    a. HLA typing is not part of regular screening in newborns as it is not a disease. HLA typing is available, but it is expensive.

15. Proposals
    a. CIRM could fund grants in cord blood research to get results that would allow for further funding from the NIH.
    b. Such funding could be in the areas such as basic science of engraftment and expansion in vivo, the use of more than one unit for transplantation, addressing HLA mismatches, the role of immune cells / natural killer cells in transplant success and other topics identified by the scientific community as the key areas for cord blood research.

C. Discussion Topics - Databanking

1. The National Institutes of Health (NIH) is making a significant effort to collect, characterize, and provide hESCs (federally approved lines) at a low price. It is unclear how well or consistently characterized all the NIH approved cell lines are, but this kind of standardization might be useful to the stem cell research community.

2. It was suggested that one of the CIRM's goals should be to promote the establishment of an internationally accessible repository of stem cell lines. CIRM can play a major role in supporting this effort, which would be an investment for the international research community.
    a. Such a repository would accept deposits and adopt a universal set of standards.
    b. While there are a number of stem cell banking efforts underway throughout the world (e.g. UK, Singapore), California would be an obvious locale for such a repository in the US, and if there is funding for it, there is potential to become the leading stem cell bank internationally. The protocols and operating procedures at this repository could become the global standard.
    c. This repository would be for both cells and information and would serve as a repository for cells and all of the accumulated, collected data. There would also need to be verification that the lines were derived using widely accepted principles.
    d. The repository would accept other researchers' results and set up an established set of standards. In this way, any cell lines that came into the bank could be measured against those standards and accepted principles. Question as to whether characterization against standards be done centrally or dispersed.

3. The mechanism for a repository can be seen in the set-up of the National Stem Cell Bank by the WiCell Research Institute.
    a. WiCell received an NIH infrastructure grant to store as many federally approved lines as they could accumulate and serve as a clearinghouse for distribution of these lines. A similar effort needs to be done for the international community (and for unapproved lines as well) to give the research community access to lines of acceptable quality.
    c. WiCell currently has 5 approved lines in its bank. The challenge is getting agreements from other entities to be allowed to be the "wholesalers" for ESC lines.
    d. With the spirit of open access, such banks will be used heavily; if we can convince people to deposit cells, it is just a matter of operating the bank.

4. It was suggested that it might be a condition of CIRM funding that any lines derived with CIRM funds need to be placed in a repository and be made broadly available.

5. There was a question about whether there is greater value in having an information repository in advance of or in addition to a stem cell repository.
   a. The main challenge is dealing with information of variable quality. If the databank could show references and have standards as to whether or not information has been published, that might be useful for those in the field but not if the quality of the data is unknown.
   b. A good model to think about is the Human Genome Project (HGP) which made it clear as to the quality of posted/linked data (e.g. uncertain, undocumented, etc. Also, a bricks and mortar project isn't needed; the HGP put everything on the web and used that as its information repository.
   c. This is a more complex project than the Human Genome Project as there are numerous different characterizations. Dr. Larry L. Smarr of UCSD has been a leader at developing internet-based complex interactive information networks.
   d. The suggestion was made that CIRM could partner with groups that are providing stem cell information resources (e.g., International Stem Cell Forum) and perhaps determine if there is a way that we could build on their efforts for the benefit of stem cell scientists in California and throughout the world.

D. Public / Additional Comments

1. A suggestion made about a possible topic for CIRM consideration and potentially future SPAC discussion: in addition to the ethical issues associated with egg donation is the issue of supply. CIRM might investigate what it can do to alleviate this issue while at the same time mitigating the associated risks.
   a. Organ donors may serve as an analogy; eggs can be collected in much the same way organs are collected from organ donors.
   b. Obtaining eggs in this way would require exploring how immature eggs can be matured for use in research. In vitro maturation has generated a lot of interest over the last decade with limited progress.
   c. The issue of egg procurement was a dominant topic of discussion during the International Society for Stem Cell Research (ISSCR) task force's deliberations over stem cell research guidelines (Note: these draft guidelines were released in June).

2. A suggestion was made that CIRM consider the use of post-mortem brain tissue to create neural brain cells; Children's Hospital of Orange County is investigating this technology.